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Injury and stress responses of adult neural crest-derived cells

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A B S T R A C T

Multipotent neural crest cells can self-renew and give rise to a plethora of neural and non-neural cell types in the vertebrate embryo. Intriguingly, cells reminiscent of such neural crest stem cells (NCSCs) have also been isolated from various postnatal and adult neural crest (NC)-derived structures. However, it has been debated whether NCSC-like cells in the adult correspond to '*in vitro* artefacts' emerging upon isolation or fulfil a physiological role *in vivo*. Here, we discuss recent findings indicating that in different adult NC derivatives, injury or stress responses induce a NCSC-like state, presumably by reprogramming differentiated cells such as Schwann cells. Thereby, injury or stress appear to endow NC-derived cells with the capacity to generate new cell types during the repair process; in addition, injury can activate a repair program in adult NC-derived cells, which promotes tissue repair or regeneration by paracrine signalling. Thus, there is increasing evidence that NCSC-like cells in NC derivatives represent an *in vivo* state implicated in distinct physiological functions in the adult organism.

1. Introduction

The neural crest (NC) is an embryonic population of cells in the dorsal part of the neural tube that migrate extensively across the embryonic body and give rise to a surprising variety of cell types (Bronner and LeDouarin, 2012; Zurkirchen and Sommer, 2017). Upon isolation, a large fraction of these cells displays multipotency and self-renewal capacity. This demonstrates that, at least in culture, many NC cells are *bona fide* neural crest stem cells (NCSCs) (Shakhova and Sommer, 2010; Dupin and Sommer, 2012). Furthermore, clonal analysis *in vivo* demonstrated that single NC cells are also able to generate multiple derivatives in the developing embryo (Bronner, 2015). Likewise, *in vivo* tracing experiments supported the notion that early migratory NC cells and NC-derived cells in peripheral nerves are self-renewing, at least for a restricted time period (Morrison et al., 1999; Baggiolini et al., 2015). These studies are in line with a growing body of evidence suggesting that NCSC features are maintained in some cells into adulthood. These cells can be activated in culture or *in vivo*, for instance, after transplantation (Shakhova and Sommer, 2010; Dupin and Sommer, 2012). In fact, almost all adult NC-derived structures comprise cells with an inherent NCSC potential, including cells in dorsal root ganglia, peripheral nerves, the gut, the skin, the heart, the bone marrow, and the cornea of the eye. Despite major advances in this field, the exact identity of the cells at the core of this plasticity is still elusive. In this review, we discuss the evidence for cellular plasticity in adult NC derivatives *in vivo*, focusing on the physiological response modes of NC-derived cells upon stress or injury in rodents. For studies on other model organisms, we would like to refer the reader to recent reviews on organ regeneration in zebrafish (Gemberling et al., 2013) (González-Rosa et al., 2017) (Pfefferli and Jaźwińska, 2015) and axolotl (Nacu and Tanaka, 2011; Uygur and Lee, 2016) as well as on the role of innervation in these systems (Kumar and Brockes, 2012).

2. Structural contribution of neural crest-derived cells to newly forming tissue

A first paradigm of how NC-derived cells respond to injury or stress involves their contribution to new tissues by (re)-differentiation. This could happen either through de-differentiation of NC-derived specialized cell types or activation of residual cells with NCSC features. This mode of response has been found in some NC derivatives *in vivo*, as summarized below.

2.1. Generation of glial and non-glial cells from injured peripheral nerves

Similar to blood vessels, peripheral nerves constitute an extensive network reaching into the most remote parts of our body. Axons of peripheral nerves are covered by both myelinating and non-myelinating Schwann cells that develop from NC-derived embryonic Schwann cell precursors (SCPs) (Jessen and Mirsky, 2005). Intriguingly, during

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embryonic development SCPs also give rise to a variety of non-glial cell types, such as melanocytes, parasympathetic neurons, adrenal medulla cells, and mesenchymal cells in the teeth (Petersen and Adameyko, 2017). Although multipotency of SCPs has not been demonstrated *in vivo* at the single cell level, it is conceivable that SCPs share many properties with migratory NCSCs. Of note, multipotent cells with NCSC properties have been isolated from both foetal and adult peripheral nerves (Kruger et al., 2002). *In vitro*, adult $p75^{+}$ NCSC-like cells were able to form multilineage colonies containing glia, neurons and myofibroblasts. Compared to embryonic NCSCs, they displayed reduced proliferation and differentiation capacities both *in vitro* and after transplantation into chick embryos. Nevertheless, based on the combined data, it has been proposed that SCPs or cells with NCSC features persist into adulthood and could be recruited when needed (Kaucká and Adameyko, 2014). Thus, SCPs might actually represent the cell pool by which "NC stemness" is maintained throughout development into adulthood.

Alternatively, differentiated Schwann cells might be endowed with the capacity for de-differentiation into SCPs/NCSC-like cells, for instance upon injury. There is strong evidence supporting this model, as Schwann cells have been shown to exhibit a remarkable plasticity and to actively participate in nerve regeneration as repair cells (Jessen and Mirsky, 2016). Upon injury to the adult nerve, mature myelinating Schwann cells adjacent to the injury and in the distal stump downregulate myelination genes, start proliferating and transit into a specific cell type that displays both aspects of de-differentiation and activation. These repair cells re-express genes characteristic for immature Schwann cells or even earlier NC derivatives. For instance, repair cells upregulate expression of tenascin-C (*Tnc*) (Fruttiger et al., 1995; Barrette et al., 2010) that encodes an ECM molecule with limited distribution in the adult (Midwood et al., 2016) and that has been shown to be important for autocrine stimulation of NC cell migration in the embryo (Tucker, 2001; Akbareian et al., 2013). Additionally, repair cells in peripheral nerves upregulate a set of injury-specific genes. These changes in gene expression are not observed during development and have been implicated in attracting immune cells, clearing myelin debris and facilitating axon regrowth. Eventually, repair cells differentiate back to myelinating or non-myelinating mature Schwann cells and, in the optimal situation, innervation of targets is restored (Jessen and Mirsky, 2016).

De-differentiation and activation of Schwann cells upon injury of adult peripheral nerves are thought to be partially regulated by c-Jun and MAPK/ERK signalling. On one hand, *c-Jun* genetic ablation, while having no apparent effect in development, remarkably leads to failure in generating repair cells after injury (Arthur-Farraj et al., 2012). In fact, c-Jun is required to suppress myelination genes and induce a Schwann cell repair programme, which is constituted by the expression of a set of neuronal growth factors and cytokines and activation of myelin autophagy (Fontana et al., 2012; Arthur-Farraj et al., 2012; Gomez-Sanchez et al., 2015). On the other hand, rapid and transient MAPK activation induces Schwann cell de-differentiation in the nerve and immune cell chemotaxis (Napoli et al., 2012). Apart from that, duration and level of Schwann cell activating signals are important for the repair process. For example, while sustained activation of MAPK/ERK leads to failure to properly bridge and restore nerve injury, genetic *c-Jun* overexpression leads to hypomyelination (Fazal et al., 2017; Cervellini et al., 2017).

The precise events driving Schwann cell activation are not fully understood. They could involve a combination of cues from cell types connected to Wallerian degeneration, such as recruited or residing immune cells, fibroblasts, endothelial cells, and neurons (Cattin and Lloyd, 2016). Additionally, given that signs of Schwann cell activation occur within minutes after injury (Guertin, 2005), mechanical damage and consequent changes in the ECM environment of the affected nerve might serve as initial trigger for switching Schwann cells from a postmitotic to a mitogenic state, before the contribution of other cell types becomes important (Belin et al., 2017). However, MAPK-activation alone without physical damage can be sufficient to initiate Schwann cell de-differentiation (Napoli et al., 2012). Subsequent migration of activated Schwann cells appears to be controlled by TGF-β, which is secreted to the injury microenvironment by fibroblasts and perhaps other cell types. This promotes organized migration of Schwann cells from the cut nerve in a crosstalk with ephrin-B signalling (Parrinello et al., 2010; Clements et al., 2017). Moreover, macrophages are recruited to the injury site where they play multiple roles (Chen et al., 2015). In response to hypoxia, for example, they can initiate angiogenesis and the newly-formed blood vessels eventually serve as pathways for Schwan cell migration (Cattin et al., 2015).

For a proper restoration of nerve function, it is just as crucial for the Schwann cells to return to a myelinating state. Sox10, Krox20 and Oct6 are key transcription factors involved in remyelination (Kuhlbrodt et al., 1998; Topilko et al., 1994; Jaegle et al., 2003). Lately, the transcriptional repressor Zeb2 was also shown to be essential for both development of mature Schwann cells and remyelination in adult mice (Quintes et al., 2016; Wu et al., 2016). Schwann cell-specific depletion of *Zeb2* derepresses negative regulators of myelination, including Sox2, Ednrb, and Notch. Furthermore, this depletion also leads to severe neuropathies and failure of remyelination following injury (Quintes et al., 2016). Wu and colleagues made similar observations and showed that repression of Sox2 and Notch-Hey2 signalling by Zeb2 is epigenetically regulated. In *Zeb2* mutants, the arrest of Schwann cells in an undifferentiated state is due to inability to recruit histone deacetylases HDAC 1 and 2 and NuRD complex (Wu et al., 2016). For a recent update on the molecular mechanisms underpinning Schwann cell plasticity, we refer to a review by Boerboom et al. (Boerboom et al., 2017).

Interestingly, Zeb2 is also a well-known inducer of epithelial to mesenchymal transition (EMT), a process observed in tumour formation and tissue injury repair (Caramel et al., 2013; Vandewalle et al., 2005; Kalluri and Weinberg, 2009). Therefore, recently described acquisition of mesenchymal features by Schwann cells upon injury or other pathological stress is in agreement with this role of Zeb2 and its expression in the peripheral glial lineage (Clements et al., 2017; Arthur-Farraj et al., 2017; Masaki et al., 2013). The suggested mesenchymal potential of glial cells is consistent with a previous study showing that foetal sciatic nerve SCPs generate endoneurial fibroblasts *in vivo* (Joseph et al., 2004). According to a recent publication, such endoneurial fibroblasts or SCPs themselves might also contribute to osteoblast and chondrocyte formation in a mouse model of bone morphogenetic protein type 2 (BMP2)-induced heterotopic ossification (Olmsted-Davis et al., 2017).

Apart from mesenchymal fates, peripheral glia have also been reported to adopt a melanocytic cell fate upon injury. Indeed, ectopic pigmentation of transected sciatic nerve has been observed at the injury site, suggesting that under certain conditions peripheral nerve cells can generate pigment cells (Rizvi et al., 2002; Adameyko et al., 2009) (Fig. 1A). Again, the exact cell type displaying this potential remains to be determined. Apart from residual SCPs, Schwann cells induced by the injury to de-differentiate could be at the origin of ectopic pigmentation in these studies. This is supported by other findings demonstrating that Schwann cells can be reprogrammed to multipotency and can generate pigmented cells *in vitro* if exposed to appropriate culture conditions (Dupin et al., 2003; Widera et al., 2011). However, peripheral nerve injury in the skin did not result in glia-to-melanocyte transdifferentiation, as shown *in vivo* by genetic fate mapping in wounded skin (Parfejevs et al., 2018). Therefore, not all nerves might contain Schwann cells able to generate pigment cells or ectopic pigmentation might depend on a specific microenvironment.

2.2. Injury-induced neurogenesis in the adult enteric nervous system

The enteric nervous system (ENS) is a structural part of the peripheral nervous system (PNS) that extensively innervates the

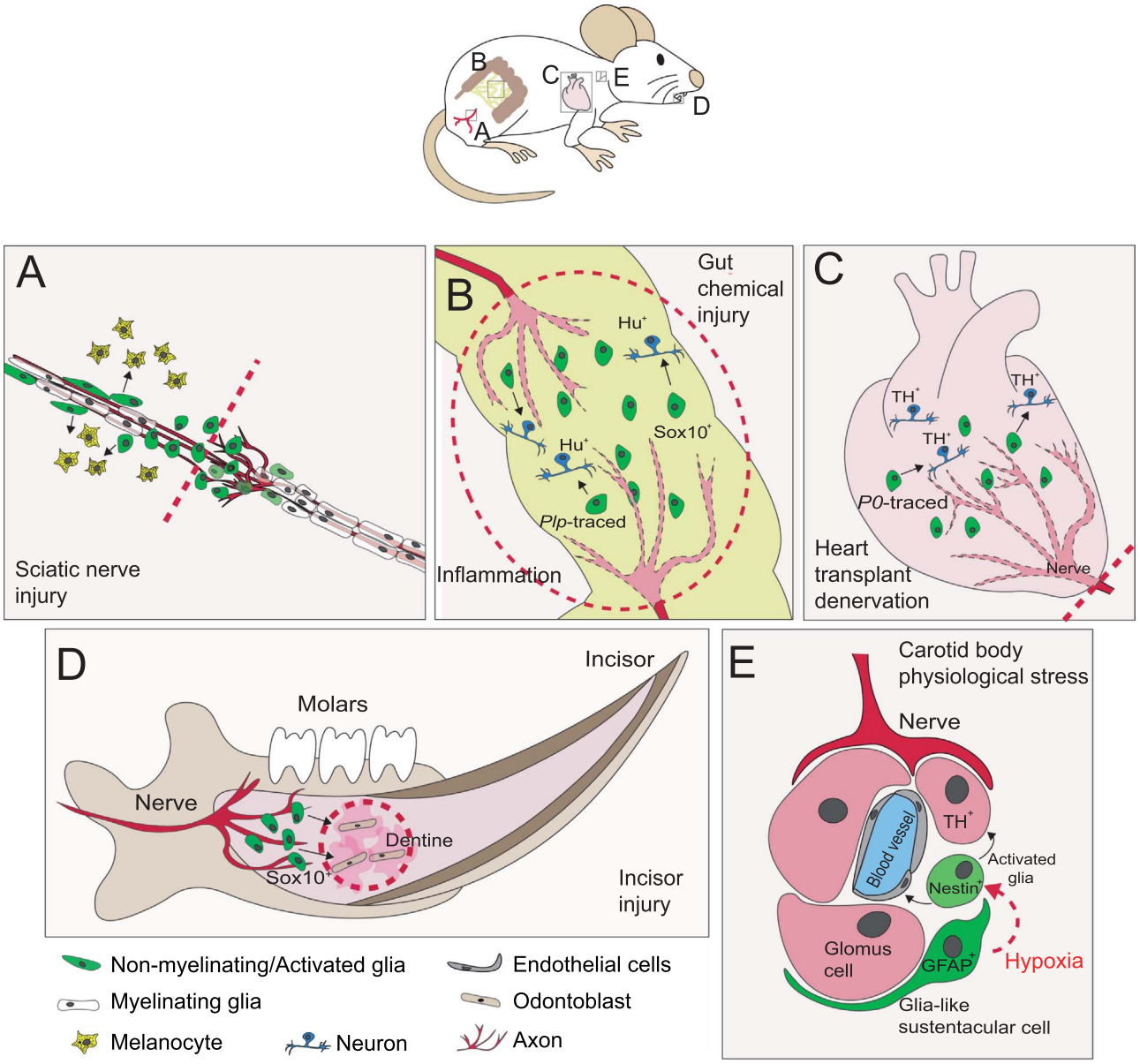

Fig. 1. Structural contribution of adult neural crest-derived cells to newly forming tissue (A) Sciatic nerve injury causes Schwann cell de-differentiation and formation of melanocytes, which leads to ectopic pigmentation observed several weeks after injury (Rizvi et al., 2002; Adameyko et al., 2009). (B) Chemical injury causes *Sox10-Cre*-traced cells to give rise to Hu^+ neurons (Laranjeira et al., 2011). Additionally, Hu^+ neurons are formed from *Plp*- and *Sox2-CreER*^{T2}-traced cells in response to inflammation in a colitis model (Belkind-Gerson et al., 2017). (C) *P0-Cre*-traced cells expand following transplantation-induced denervation and give rise to TH^+ neurons (Tamura et al., 2016). (D) NC-derived Schwann cells give rise to mesenchymal cells including odontoblast-like cells, that deposit mineralized matrix to form new dentine after tooth injury (Kaukua et al., 2014). (E) Hypoxia in the carotid body causes activation of glia-like sustentacular cells that turn into multipotent precursors and give rise to neuron-like TH^+ glomus cells and GSA I^+ endothelial cells (Pardal et al., 2007; Annese et al., 2017).

digestive system and ensures peristaltic and secretory functions of the gut (Furness et al., 2013). Several years ago, the adult rodent gut was shown to contain cells reminiscent of NCSCs, although these ENS NCSCs displayed reduced stem cell properties when compared to their embryonic and foetal counterparts (Kruger et al., 2002). In line with these findings, neurogenic progenitors have also been isolated from human foetal and adult ENS (Rauch et al., 2006; Metzger et al., 2009).

This sparked interest in the potential endogenous function of the NCSC-like cells under normal and pathological conditions. Previous observations, for instance of abnormally innervated tissue in Crohns disease, pointed towards the possibility that neurogenesis could occur in the adult gut (Geboes and Collins, 1998). Subsequently, it was demonstrated that neurogenesis can be pharmacologically induced in postnatal ENS. In response to 5-hydroxytryptamine 4 (5-HT_4), cells of supposedly glial fate gave rise to cells with neural precursor features which were positive for Sox10 and Phox2b (Liu et al., 2009). Laranjeira and colleagues used fate-mapping experiments to show that Sox10-expressing NC-derived cells generate the majority of enteric glia and neurons during development. Under normal conditions, the neurogenic potential of these cells continues postnatally, but ceases with age (Laranjeira et al., 2011). Strikingly, in response to chemical injury to myenteric ganglia with the cationic detergent benzalkonium chloride, Sox10-lineage cells displayed plasticity and gave rise to glia as well as neurons in the adult mouse gut (Fig. 1B). In contrast, another study focused on adult neurogenesis in the gut using BrdU incorporation and found no substantial evidence for neurogenesis under various physiological and experimental stress conditions. These included different diet regimens, injury and inflammation, suggesting that *de novo* neurogenesis might only occur under certain circumstances (Joseph et al., 2011).

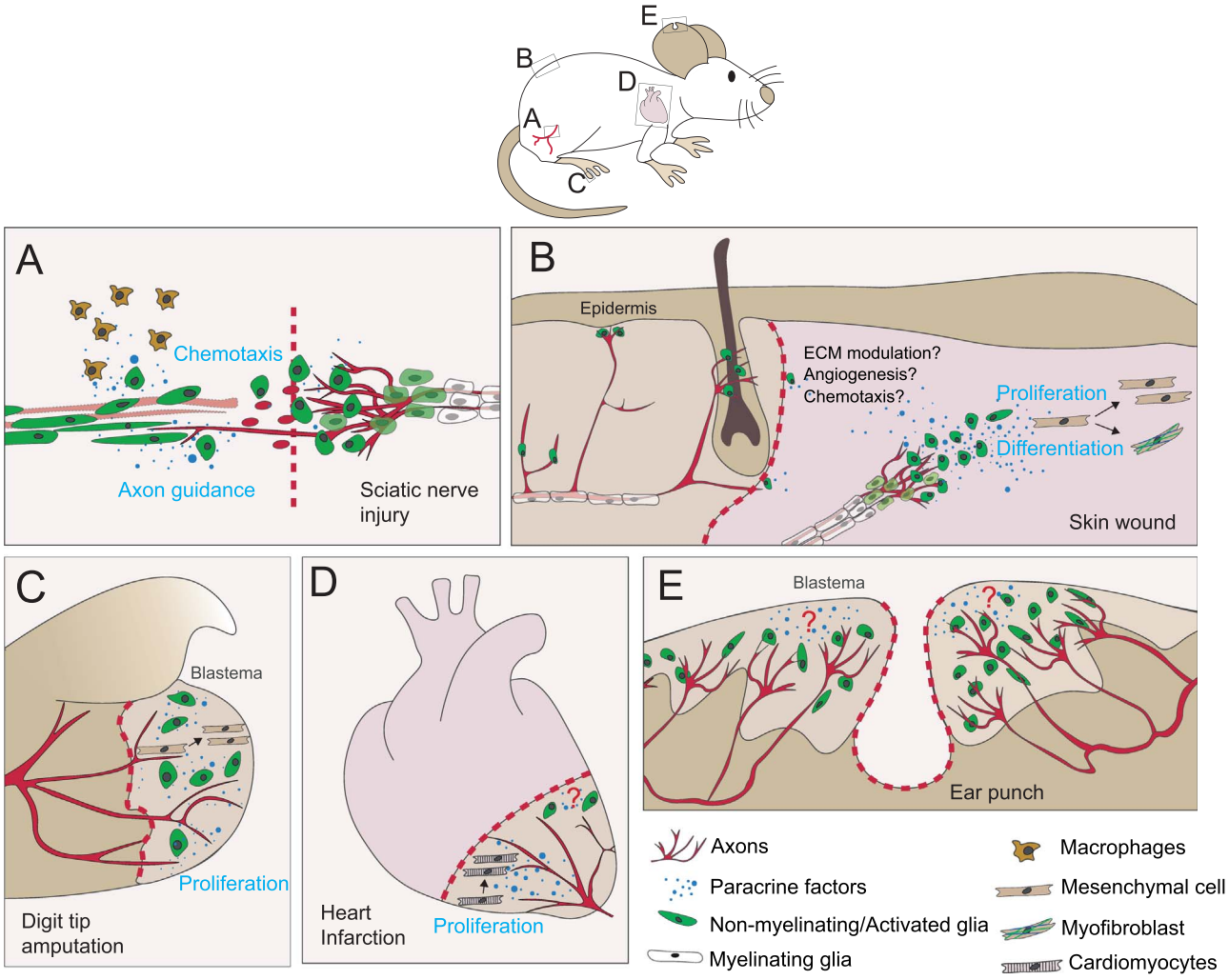

Fig. 2. Neural crest-derived cells supporting tissue repair by paracrine signalling (A) Shortly after sciatic nerve trauma de-differentiated Schwann cells secrete a cocktail of cytokines and chemokines including MCP1, LIF and TNFα to attract immune cells and a set of neurotrophic factors, adhesion molecules and ECM molecules to facilitate axon regrowth (Jessen and Mirsky, 2016). (B) Skin injury activates local peripheral nerve-associated glia that upregulate a set of genes coding for paracrine factors previously implicated in regeneration and repair. Glial cells stimulate proliferation of mesenchymal cell pool and differentiation to more contractile phenotypes to accelerate wound healing. Ablation of these cells leads to delayed wound closure (Johnston et al., 2013; Parfejevs et al., 2018). (C) The blastema of the regenerating digit tip is innervated by FGF2-secreting axons and populated by activated Schwann cells that provide PDGF-AA and OSM. In both instances, paracrine factors stimulate proliferation of mesenchymal cells of blastema and foster regeneration (Takeo et al., 2013; Johnston et al., 2016). (D) Cardiac innervation provides NGF to the regenerating heart to stimulate cardiomyocyte proliferation. Pharmacological inhibition or denervation impairs heart regeneration after infarction (Mahmoud et al., 2015). The potential role of Schwann cells in this process remains to be investigated. (E) In some mammals ear punch leads to formation of blastema and regeneration (Buckley et al., 2011; Gawriluk et al., 2016). However, the role of innervation and glia in this process remains to be elucidated.

Following up on these observations, Uesaka and colleagues provided compelling evidence that a subset of *Dhh-Cre*-traced Schwann cell precursors (SCPs) arriving at the gut *via* extrinsic innervation contribute to neurogenesis in the juvenile mouse ENS alongside enteric NC-derived glia (Uesaka et al., 2015). Differentiation of $Sox10^{+}$ SCPs to $Phox2b^{+}$ neurons occurs prenatally and postnatally (until stage p21) and contributes to approximately 5% of the submucosal ganglion neurons in the small intestine and around 20% of the neurons in myenteric and submucosal ganglia of the colon. The physiological relevance of this process is underpinned by the fact that loss of *Dhh-Cre*-traced neurons impacts the structural integrity of the ENS. Interestingly, a study on evolutionary origins of the ENS demonstrated that enteric neurons of the sea lamprey, a jawless vertebrate, are not derived from migrating vagal NC cells. Instead, a late-migrating population of trunk NC cells associated with nerves and reminiscent of SCPs populates the gut wall and generates ENS neurons in these early vertebrates (Green et al., 2017). Thus, a population of SCPs observed by Uesaka and colleagues (Uesaka et al., 2015) might represent an evolutionary conserved cellular population that was replaced to a large extent by cells from the vagal portion of the NC in jawed vertebrates (Green et al., 2017). Moreover, it cannot be excluded that the above-mentioned neurogenic potential of adult ENS cells, observed for example upon chemically induced tissue damage (Laranjeira et al., 2011), is associated with activation of SCPs from nerves innervating the gut.

One of the major causes of injury in the ENS is inflammation, which can lead to ENS structural abnormalities including nerve fibre hypertrophy and glial hyperplasia (Geboes and Collins, 1998). Recently, it was demonstrated that enteric glia traced by using *Sox2*- and *Plp-CreER^{T2}*-mediated recombination can give rise to neurons in a colitis model (Belkind-Gerson et al., 2017) (Fig. 1B). Thereby, a fraction of ENS glia, negative for the neural progenitor marker c-Ret, appeared to transdifferentiate into excitatory neurons without newborn cells entering cell division. These findings could explain why BrdU incorporation assessment previously failed to identify neurogenesis in inflammation models (Joseph et al., 2011).

In contrast, the failure to detect newly forming neurons by BrdU incorporation assays performed by Joseph et al. is difficult to reconcile with another study that recently reported a dynamic balance between neuronal death and neurogenesis in the myenteric plexus of the adult

small intestine ENS (Kulkarni et al., 2017). Contrary to other observations (Joseph et al., 2011; Laranjeira et al., 2011; Belkind-Gerson et al., 2017), Kulkarni et al. detected a high turnover rate of ENS neurons in a steady state and identified p75$^+$ Nestin$^+$ NC-derived progenitors to continuously proliferate and generate neurons to replace dying ones. These progenitors were reported to be negative for Sox10, suggesting that the enteric progenitors are not glial cells.

Taken together, these observations strongly suggest plasticity of NC-derived cells in the digestive system. Cells with NCSC/SCP features as well as non-glial progenitor cells have been proposed to participate in homeostatic and injury-driven neurogenesis in the adult gut. However, *in vivo* genetic cell fate mapping using multiple tracers suggest that, contrary to culture conditions, gut NC-derived cells apparently do not contribute to cells with a mesenchymal phenotype, even when subjected to injury (Laranjeira et al., 2011; Uesaka et al., 2015).

2.3. Activation of neural crest-derived cells in the heart

In some vertebrates like zebrafish and salamanders injured cardiac tissue can be readily replaced by new cardiomyocytes even in the adult organism (González-Rosa et al., 2017; Uygur and Lee, 2016). In adult mammals, however, injury-triggered formation of new contracting cells is compromised by overriding fibrosis, leaving a relatively short window during foetal and neonatal stages, in which endogenous heart regeneration can be studied (Tzahor and Poss, 2017). The NC contributes to several tissues in the heart, including the outflow tract and autonomic innervation (Santini et al., 2016). The main constituents of heart innervation are postganglionic sympathetic fibres and parasympathetic neurons relaying vagal inputs, as well as components of intrinsic cardiac innervation (Hasan, 2013). Similar to regeneration in other organs, the efficiency and extent of heart regeneration has been linked to innervation (White et al., 2015; Mahmoud et al., 2015). Specifically, innervation is important in regeneration after cardiac injury, where nerve-derived factors, such as nerve growth factor (NGF), were demonstrated to promote cardiomyocyte proliferation of recovering zebrafish and neonatal mouse heart (Mahmoud et al., 2015) (Fig. 2).

Previous studies performed in rodents have also highlighted the presence of NC-derived cells displaying marks of undifferentiated NCSCs in the adult heart. These NCSC-like cells are able to form spheres in culture and display multilineage differentiation potential *in vitro* and upon transplantation (Nakamura et al., 2006; Tomita et al., 2005; El-Helou et al., 2008). More recent findings suggest that c-Kit, a proposed cardiac stem cell marker, also labels cardiac NC cells in the heart (Hatzistergos et al., 2015). Despite contradicting results regarding the ability of c-Kit$^+$ progenitors to generate cardiomyocytes (Beltrami et al., 2003; Van Berlo et al., 2014; Sultana et al., 2015), Hatzistergos and colleagues provided evidence that c-Kit$^+$ NC-derived cells possess cardiomyogenic potential (Hatzistergos et al., 2015). Given the presence of c-Kit$^+$ progenitors in the adult heart, it is plausible that modification of the microenvironment could unravel the differentiation potential of c-Kit$^+$ cells in injury settings.

In human patients, it is known that, after heart transplantation, limited reinnervation can take place within the following years, which is associated with improved heart rate and contractile function (Bengel et al., 2001). Based on this, an interesting recent study used a mouse model of ectopic heart transplantation to follow the fate of NC-derived cells in cardiac tissue (Tamura et al., 2016). A NC-derived population traced by *P0-Cre* was shown to contain a fraction of TH$^+$ cells present in the heart before the onset of sympathetic innervation, as early as E10.5. This population decreased upon sympathetic innervation, but persisted into adulthood. Interestingly, ectopic mouse heart transplantation causing sympathetic denervation led to an immediate expansion of intramyocardial *P0-Cre* traced cells in the transplanted heart. This event was followed by an increase in the number of traced TH$^+$ cells, possibly in response to increased NGF levels (Tamura et al., 2016). Thus, a resident NC-derived cell population, perhaps together with glial cells that lost axonal contacts due to denervation, seems to participate in restoration of cardiac sympathetic activity by differentiation into TH$^+$ cells (Fig. 1C). Given these findings, it would be intriguing to study whether NC-derived cells associated with the intrinsic adrenergic system or extrinsic autonomic innervation also participate in heart regeneration processes after acute injury.

2.4. Schwann cells at the origin of mesenchymal cells in adult teeth

Teeth are formed in a process of interaction between mesenchymal and epithelial tissues. Similar to other cranial structures, tooth mesenchyme has long been known to be derived from the cranial NC (Jernvall and Thesleff, 2012). In mammals, teeth have limited regeneration ability. In some species, however, constantly growing teeth make up for this disadvantage. Kaukua and colleagues used a mouse model of continuously growing incisor teeth to demonstrate that a significant portion of mesenchymal stem cells (MSCs) that form dental pulp and odontoblasts in fact stem from dental nerve-associated SCPs (Kaukua et al., 2014). Specifically, *Plp-CreER^{T2}* and *Sox10-CreER^{T2}* traced Schwann cells located at the MSC niche generated new MSCs that turned into pulp cells and odontoblasts in the adult growing incisor. Of note, also after injury, genetically traced glial cells gave rise to odontoblasts forming new dentine (Kaukua et al., 2014) (Fig. 1D). This is a further example of SCPs residing in local nerves and serving as endogenous NCSC-like cells in the adult, this time displaying osteogenic potential after injury.

2.5. New tissue formation upon a physiological stress response in the carotid body

The carotid body is a NC-derived sympathoadrenal oxygen-sensing organ (Pearse et al., 1973). In this organ, neuron-like glomus cells are responsible for sensing changes in oxygen partial pressure. In fact, it has been known for a long time that hyperplasia of glomus cells can occur throughout the life of people living at high altitudes (Arias-Stella and Valcarcel, 1976). Physiological stress, which for this organ is hypoxia, triggers changes in different cells types in the carotid body. Pardal and colleagues showed that GFAP$^+$ glia-like sustentacular cells enter the cell cycle and give rise to new glomus cells with dopaminergic features (Pardal et al., 2007). Later it was demonstrated that, in the process of adaptation to low oxygen, the same cells can also generate endothelial cells, apart from undergoing neurogenesis (Annese et al., 2017). Vascular factors including HIF-2α and erythropoietin produced by the carotid body are proposed candidates in promoting this effect. Thus, adult NCSC-like cells found in the carotid body could represent a multipotent cell population with a relevant physiological role, capable in stress situations of both neuroectodermal and mesectodermal differentiation (Fig. 1E).

3. Neural crest-derived cells supporting tissue repair by paracrine signalling

According to a second paradigm of injury and stress response in NC derivatives, cells of NC origin respond to injury but without apparent transition to other cell fates. Rather, injury- or stress-activated cells participate in repair processes through secretion of factors influencing their environment. Apart from a quite well established role of Schwann cells in supporting peripheral nerve repair by paracrine signalling, this mode of response has recently been reported in other injury models. Of note, most of the observations were associated with injury-activated peripheral glial cells.

3.1. Sciatic nerve regeneration by nerve-derived repair cells

As discussed in the previous section, Schwann cells in the PNS respond to injury by adopting a repair cell phenotype with features not observed during development. These cells are highly secretory and are able to modify the environment in order to control inflammation and axon guidance. After injury, they start secreting a number of cytokines and chemokines such as TNFα, LIF, MCP1, interleukins and others, which help recruiting monocytes that eventually turn into macrophages (Gaudet et al., 2011). To promote axonal growth, these cells upregulate genes coding for a set of neurotrophic growth factors including GDNF, BDNF, NT-3, NRG1, NGF, and others (Boyd and Gordon, 2003). Repair cells also produce ECM components, most notably laminins that facilitate neurite outgrowth (Chen et al., 2007; Gonzalez-Perez et al., 2013) (Fig. 2A).

Although much more efficient than in the central nervous system (CNS), PNS regeneration in human after trauma is limited (Grinsell and Keating, 2014). Use of Schwann cells for transplantation holds considerable promise for treatment of CNS and peripheral nerve trauma and neuropathies (Tetzlaff et al., 2011; Lehmann and Höke, 2010). However, a deeper understanding of the molecular repair mechanisms could allow more precise manipulation of the regeneration process in the PNS (Boerboom et al., 2017). For example, temporary inhibition of HDAC 1,2 was found to boost formation of repair cells after nerve injury (Brügger et al., 2017). For an in-depth discussion on repair cells in peripheral nerves, see the recent review by Jessen and Mirsky (Jessen and Mirsky, 2016).

3.2. The role of injury-activated peripheral glial cells in skin repair

Cutaneous wound healing is a complex process that involves an intricate interplay between different cell types aiming at restoration of injured tissue function (Gurtner et al., 2008; Eming et al., 2014). Healing phases are similar across different animal species and include inflammation, re-epithelialization, granulation tissue formation, and matrix remodelling, yet the outcome can be different. In zebrafish, for example, full-thickness wound healing response yields nearly complete restoration of the original tissue (Richardson et al., 2013), while in axolotls it leads to complete regeneration (Seifert et al., 2012). Likewise, wounds in mammals at early foetal stages heal by complete regeneration of the original tissue. However, with the establishment of a mature immune system this ability is lost and wounding leads to scar-forming healing (Larson et al., 2010). Notable exceptions include *de-novo* hair follicle formation reported to occur after large skin wounds in mice (Ito et al., 2007) and complete regeneration of skin in certain rodent species after skin shedding (Seifert et al., 2012).

Since skin is a densely innervated organ, it has been presumed that wound repair potentially depends on NC-derived innervation. Nevertheless, there are reports suggesting both importance and dispensability of innervation for the outcome of wound healing (Harsum et al., 2001; Barker et al., 2006; Rinkevich et al., 2014). One potential effect of innervation is associated with a secretory function of axons that provide a set of neuropeptides for the wounded skin (Ashrafi et al., 2016). Another role could be attributed to involvement of nerves in maintenance of stem cells in skin appendages. For example, sonic hedgehog derived from the perineurial niche is necessary for maintenance of $Gli1^+$ hair follicle stem cells that become epidermal stem cells upon injury and for stem cell homeostasis in the touch dome (Brownell et al., 2011; Xiao et al., 2015).

Recent evidence supported a crucial role of Schwann cells, a major cellular constituent of innervation, as another player in cutaneous injury response. Presence of Schwann cells found in close proximity to hair follicles as part of follicular innervation was shown to correlate with expression of Lgr6, a marker of epidermal stem cells important for wound re-epithelialization (Liao and Nguyen, 2014; Snippert et al., 2010). These findings suggest a role for Schwann cells in niche maintenance. Yet Johnston and colleagues (Johnston et al., 2013) have lately proposed a different mode of Schwann cell participation in skin repair. These authors demonstrated that genetic depletion of $Sox2^+$ cells interferes with normal wound healing in the adult mouse. $Sox2^+$ cells, among other cell types, likely represent de-differentiated Schwann cells appearing in the wound bed after injury. The delay in full-thickness wound closure observed in this study was accompanied by a decreased number of cycling $Ki67^+$ cells at the leading edges of the closing wound. These data are consistent with the idea that $Sox2^+$ cells could exert their function in wound healing through secretion of factors promoting cell proliferation in the wound bed (Johnston et al., 2013) (Fig. 2B).

In agreement with this hypothesis, recent work performed in our laboratory demonstrated a role of genetically traced peripheral glia in adult skin wound healing (Parfejevs et al., 2018). In a mouse model of skin full-thickness wound, glial cells became activated and lost markers of differentiated Schwann cells. Subsequently, activated glial cells emerged from apparently injured nerves and started to proliferate and to populate injured tissue. These injury-activated cells displayed markers characteristic for NCSCs and glial repair cells (Jessen and Mirsky, 2016), including expression of p75, pERK and c-Jun. Although the factors inducing glial cell activation remain to be determined, injury to peripheral nerves in the absence of any other cell types appears to be sufficient to trigger de-differentiation into NCSC/glial repair cells (Parfejevs et al., 2018). Therefore, these cells might correspond to some of the multipotent NCSC-like cell populations that have previously been isolated from adult skin using different cell culture methods (Toma et al., 2005; Belicchi et al., 2004; Sieber-Blum et al., 2004; Amoh et al., 2005; Wong et al., 2006; Etxaniz et al., 2014; Gresset et al., 2015; reviewed in Shakhova and Sommer, 2010).

Intriguingly, RNA sequencing performed on lineage-traced glial cells isolated from skin wounds suggests that these cells could secrete proteins previously implicated in tissue repair and in regulating various processes, such as TGF-β signalling, angiogenesis, chemotaxis, and others (Fig. 2B). This appears to be functionally relevant, because genetically induced loss of glia led to delayed wound closure and decreased wound contraction, associated with decreased myofibroblast activity (Parfejevs et al., 2018). In contrast, increasing the number of injury-activated glia in the wound bed by genetic means resulted in enhanced fibroblast to myofibroblast transition. Furthermore, in co-culture experiments, it was shown that injury activated glia promote myofibroblast formation in a paracrine manner by modulation of TGF-β signal activity. Given the presence of different fibroblast subtypes in the skin (Driskell et al., 2013; Rinkevich et al., 2015), it will be interesting to investigate whether de-differentiated Schwann cells in the wound exert their function by acting on a particular type of fibroblasts in the wound. Hence, apart from axonal signals, nerve-derived de-differentiated peripheral glia resembling SCPs/NCSCs emerge as paracrine effectors of skin repair processes.

Similar to what we have discussed above in the section on peripheral nerve regeneration, the exact events that turn on Schwann cell plasticity in the wounded skin are unknown. Possibly, the various glial cell subtypes present in the skin might differentially respond to activation cues. For example, degeneration of myelinated motor axons after ventral rhizotomy caused proliferation of non-myelinating Schwann cells in neighbouring intact nerves, while Schwann cells of myelinated axons did not enter the cell cycle (Murinson et al., 2005). The activation signals might in part correspond to those known to be important for activation of other cell types in the wound, such as fibroblasts and endothelial cells that also go through phenotypical changes, proliferate, and migrate in response to injury (Greaves et al., 2013). A variety of growth factors and chemokines, including FGF-2, PDGF, IGF, TNF-α, IL-6 and many others derived from the recruited immune cells and freshly-formed haemostatic clot, appear early at the injury site and could activate mitogenic pathways in glial cells (Greaves et al., 2013; Jessen and Mirsky, 2005; Eccleston, 1992; Qin et al., 2008;

Demir et al., 2016). Additionally, early injury signals, such as reactive oxygen species, polyunsaturated fatty acids or damage-associated molecular patterns from lysing cells could play a part in activation (Niethammer, 2016). Subsequently, similar to wound fibroblasts that migrate in response to TGF-β (Postlethwaite et al., 1987; Acharya et al., 2008), activated glial cells might populate the wound by performing EMT, as has been shown for NC cells early in development (Theveneau and Mayor, 2012) and Schwann cells after PNS injury (Clements et al., 2017).

In cutaneous injury settings, the presence of epithelial cells adds another layer of complexity. Keratinocytes are known to be involved in active interactions with different wound granulation tissue cells (Werner et al., 2007; Leoni et al., 2015). In animals capable of regeneration, signals from the wound epidermis are important for induction of the blastema and epithelial-blastemal interactions have been shown to recruit nerves to the injury site (Campbell and Crews, 2008; Takeo et al., 2013). *Fos* and *c-Jun* belong to the early response genes activated in wound keratinocytes allowing proliferation and migration of the epidermis (Martin and Nunan, 2015). Similarly, AP-1 family members have an early peak of expression following Schwann cell activation in the PNS (Arthur-Farraj et al., 2017). As part of an AP-1 complex, c-Jun is responsible for the onset of a repair program in Schwann cells (Arthur-Farraj et al., 2012) and is also prominently expressed in various wound granulation tissue cells and particularly in injury-activated nerve bundles after skin injury (Parfejevs et al., 2018). Together, this could point to some common wound healing/regeneration signals and cell reaction mechanisms that may govern cell plasticity and function in a context-dependent manner (Owlarn et al., 2017; Jessen et al., 2015).

3.3. Peripheral glial cells in mammalian regeneration models

A great deal of knowledge about regeneration comes from studies of animals that have significant endogenous regeneration capacity like planarians and amphibians. Some planarians are unique in their ability to regenerate the whole organism from a small original part (Reddien and Sánchez Alvarado, 2004), while some amphibian species are able to regenerate whole limbs and other organs, such as brain, heart and the eye (Godwin and Rosenthal, 2014). Regeneration of the limbs in amphibians proceeds through several stages, including wound healing, activation of tissue progenitors, and formation of new limbs, a process reminiscent of embryonic development (Tanaka, 2016). Progenitor cells forming different limb tissues during regeneration are located in a special zone called blastema and seem to be morphologically homogeneous. Yet the cells in the blastema represent a set of restricted tissue progenitors that can retain memory of their developmental origin and, in some cases, even spatial memory (Kragl et al., 2009).

Mammals, including humans, possess a limited ability to fully restore the original tissue upon damage. However, there are several prominent examples of injury-triggered tissue regeneration in adult mammals (Muneoka et al., 2008). These encompass ear punch regeneration, which has first been described in rabbits and later in other lagomorph and rodent models like MRL/MpJ mice and African spiny mouse (Metcalfe et al., 2006; Clark et al., 1998; Gawriluk et al., 2016), as well as the generation of the mouse digit tip after amputation (Borgens, 1982). Spontaneous regeneration of human digit tips has also been documented in several cases both in children and adults (Illingworth, 1974; Lee et al., 1995; Rinkevich et al., 2015).

The digit tip regeneration model has lately received particular attention, with several groups identifying important components for regeneration (Han et al., 2008; Fernando et al., 2011; Rinkevich et al., 2011). During this process, a structure similar to amphibian blastema is formed (Seifert and Muneoka, 2018). Takeo et al. (2013) have identified nail stem cells to be important drivers of digit blastema formation. After the amputation of the finger at the level of the terminal phalange but distal from the nail base, nail stem cells get activated in a Wnt-dependent manner and new nail is formed with a differentiation gradient starting from the base of the nail. Newly-forming nail acts in a similar manner as blastemal epidermis in lower vertebrates. It signals to the blastema to attract nerves by secreting nerve-guiding cues, while nerves in turn provide FGF-2 for proliferating mesenchymal blastemal cells (Takeo et al., 2013) (Fig. 2C). This study highlights the importance of innervation and paracrine signalling in mammalian regeneration, similar to what has long been observed in amphibians, where the extent of innervation can be directly correlated with the ability to regenerate (Endo et al., 2004; Kumar and Brockes, 2012; Farkas and Monaghan, 2017). In mammals, the link between innervation and regeneration was further supported by studies revealing that digit denervation results in retardation of regeneration (Mohammad and Neufeld, 2000; Rinkevich et al., 2014).

Comparable to skin wound healing, Schwann cells have been functionally implicated in the process of tissue regeneration. In salamander wounds, Schwann cells separate from nerves, migrate into the blastema, and secrete newt anterior gradient protein (nAG) that mediates blastemal epithelium formation (Kumar et al., 2007). An exciting recent study showed that also in adult mice upon digit amputation, Schwann cells are found within the blastema and secrete factors, such as PDGF-AA and Oncostatin M (OSM), that promote mesenchymal linage proliferation (Johnston et al., 2016) (Fig. 2C). Furthermore, digit tip regeneration in the denervated limb can be rescued to a certain extent by rat SCP transplantation or by the addition of the mentioned factors (Johnston et al., 2016). Importantly, the study also provides a list of SCP-associated paracrine factors that might contribute to the pool of ligands promoting tissue formation during regeneration. Thereby, the paracrine effects elicited by injury-activated peripheral glia could be direct as shown for PDGF-AA and OSM or mediated by recruited cells as seen in sciatic nerve injury (Tofaris et al., 2002). Furthermore, a paracrine effect could also be exerted through modification of the ECM towards an extracellular environment more favourable for regeneration (Gawriluk et al., 2016). Of note, *Pdgfa* was not found among differentially expressed genes after injury in other studies in sciatic nerve and skin (Barrette et al., 2010; Clements et al., 2017; Parfejevs et al., 2018). This points to variations in the mode of response that might depend on the environment or on the presence of different Schwann cell subtypes associated with nerves in distinct organs or tissues. The latter idea is supported by findings showing that growth factor expression induced in Schwann cells upon denervation can depend on the type of the nerve (sensory, motor) and the location in the body (Hoke, 2006; Brushart et al., 2013). It is further important to consider that these differences can persist even upon isolation (Brushart et al., 2013). Finally, acknowledging a proposed overlap between processes in development and tissue repair (Martin and Parkhurst, 2004), it would be interesting to investigate whether some of the paracrine functions of NC-derived cells in injury are in place during NC or SCP migration in the embryo.

Interestingly, denervation of the digit tip prior to amputation leads to absence of peripheral glia in the forming blastema and failure of proper regeneration even though glial cells remain scattered in the distal stump of a cut nerve close to the injury (Johnston et al., 2016). This suggests an involvement of both axonal and Schwann cell-derived signals in regeneration and might reflect failure of axon-deprived Schwann cells to proliferate or migrate towards the blastema. Similarly, in continuously-growing mouse incisors, denervation leads to failure of genetically traced glial cells to form mesenchymal progeny (Kaukua et al., 2014). Other nerve-derived ligands that have been previously implicated in regeneration include neurotrophic factors, BMP, FGF and WNT family members (Mahmoud et al., 2015; Farkas et al., 2016; Mullen et al., 1996; Mescher et al., 1997; Takeo et al., 2013; Satoh et al., 2016). It would be interesting to further dissect the precise origin of these factors and to elucidate the interplay between Schwann cells and axons in regenerating tissue.

Another well-known structure that regenerates with blastema

formation in some mammals is the ear pinna. Hyperinnervation and nerve dependence have also been implicated in the formation of a blastemal structure following ear punch. However, the precise role of activated glial cells in this process remains to be demonstrated (Buckley et al., 2011; Seifert et al., 2012) (Fig. 2E). Given the different cellular composition and innervation of digit tip and ear pinna blastemas, NC-derived cells might rely on distinct mechanisms supporting regeneration of these tissues.

3.4. Concluding remarks

Recent literature has pointed to a growing number of tissues, in which endogenous adult NC-derived cells appear to respond to injury and stress by acquisition of a new cell fate in a process that likely involves de-differentiation and *in vivo* reprogramming (Fig. 1). Alternatively, injury-induced de-differentiation to a cellular state reminiscent of NCSCs can activate a repair program associated with secretion of tissue repair factors (Fig. 2). Thus, accumulating evidence summarized in this review suggests that multipotent NCSC-like cells persist or can be induced *in vivo*, although this needs to be proven on a single cell level. Likely, these cells correspond to those cells that have been isolated by various laboratories from many adult structures and shown to display NCSC features and plasticity *in vitro* (Shakhova and Sommer, 2010).

It is conceivable that NC-derived structures beyond the ones discussed in this review could harbour cells with endogenous plasticity and stress-response/repair function. Notably, several tissues are known, in which homeostasis and maintenance of the stem cell niche are supported by innervation, such as the bone marrow (Yamazaki et al., 2011), hair follicles of the skin (Brownell et al., 2011; Xiao et al., 2015), and the cornea (Ueno et al., 2012). Therefore, it is possible that injury responses in these systems might also involve activated glia providing paracrine support for tissue repair. Likewise, peripheral glia not only generate dental mesenchymal cells during development, homeostasis and upon injury (Kaukua et al., 2014), but could potentially be involved in homeostasis of mesenchymal cells in teeth by factor secretion (Zhao et al., 2014). Thus, it is probable that in this setting NC derivatives could promote tissue healing both by contribution to new cell types and paracrine effects on the microenvironment.

Moreover, the capacity to promote tissue repair by paracrine signalling might not only be inherent to injury-activated peripheral glia. For instance, NC-derived Nestin^{+} mesenchymal stem cells (MSCs) have been found to support the hematopoietic stem cell HSC niche (Isern et al., 2014). Likewise, other cells than peripheral glia might display cellular plasticity in response to stress or injury. For example, in some tissues, NC cells can give rise to pericytes (Etchevers et al., 2001; Trost et al., 2016; Radomska and Topilko, 2017), which themselves have been proposed to be a source of MSCs (Crisan et al., 2008). Furthermore, at least in culture, differentiated pigment cells are able to undergo de-differentiation and to produce new cell types, such as Schwann cells (Real et al., 2006). Hence, the origin and exact nature of NC-derived 'repair cells' might be dependent on the tissue and/or the cue triggering their activation. Further studies of the cellular states induced by injury and stress in NC derivatives will not only give us deeper insights into the biology and potential of NC-derived cells in the adult, but will also increase our understanding of tissue repair mechanisms. This knowledge could offer means to guide the repair process, for example, by direct cell transplantation, or local application of products identified in the secretome of these cells. Alternatively, advantage could be taken of compounds that either control activation of NC-derived cells (*e.g.* Schwann cells) or directly act on targets of bioactive molecules secreted by these cells. This could be particularly relevant for conditions where normal tissue repair is compromised, leading to either chronic non-healing wounds such as diabetic ulcers or hypertrophic scar and keloid formation.

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